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The ESCAPE-NET project

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Clinical paper

Determinants of occurrence and survival after sudden cardiac arrest—A European perspective: The ESCAPE-NET project[☆]

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ABSTRACT

Aims: The ESCAPE-NET project (“European Sudden Cardiac Arrest network– towards Prevention, Education and New Effective Treatments”) aims to study: (1) risk factors and mechanisms for the occurrence of sudden cardiac arrest (SCA) in the population, and (2) risk factors and treatment strategies for survival after SCA on a European scale.

Methods: This is an Horizon2020 funded program of the European Union, performed by a European public-private consortium of 16 partners across 10 EU countries. There are 11 deep-phenotyped SCA cohorts for the study of risk factors and treatment strategies for survival after SCA, and 5 deep-phenotyped observational prospective population cohorts for the study of risk factors for occurrence of SCA. Personalized risk scores for predicting SCA onset and for predicting survival after SCA will be derived and validated.

Results: The 11 clinical studies with SCA cases comprise 85,790 SCA cases; the 5 observational prospective population cohorts include 53,060 subjects. A total of 15,000 SCA samples will be genotyped for common and rare variants at the Helmholtz Zentrum München (Germany) using the Illumina Global Screening Array which contains > 770,000 SNPs, and after imputation, a database of an estimated > 9 million variants will be available for genome wide association studies. Standardization of risk factors definition and outcomes is ongoing. An Executive Committee has been created along with a Collaboration Policy document.

Conclusion: ESCAPE-NET will complement ongoing efforts on SCA outside Europe and within Europe including the EuReCa project.

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Introduction

Despite recent improvements in cardiopulmonary resuscitation and post-resuscitation care, survival after out-of hospital sudden cardiac arrest (SCA) remains as low as 10% on average when considering the whole spectrum of SCA including SCA with no attempts of resuscitation by Emergency Medical Services [1]. The challenges ahead of us include a better capacity to identify individuals from the population who are at risk of SCA, improvement in resuscitation strategies, and a better understanding of the mechanisms of SCA.

Multiple studies have reported on individual risk factors for SCA occurrence including traditional acquired risk factors or comorbidities (diabetes, myocardial infarction, hypertension, smoking, obesity) [2], familial predisposition [3] or neural control of heart rhythm [4] (Fig. 1 left). Still, we lack sensitive risk stratification algorithms for SCA [5]. Previous attempts at risk prediction modelling were conducted in specific subgroups such as patients with acute myocardial infarction [6] or, when addressing the general population, considered a limited set of covariates [7]. Moreover, while evidence for a role of hitherto little studied risk factors has recently emerged (socio-economic and psychosocial stress [8], and environmental factors such as air pollution [9] and roadway proximity [10]), the extent to which these emerging factors contribute to the occurrence of SCA beyond the effect of already known risk factors remains to be studied. Finally, the possible effect of drugs on SCA occurrence and their interaction with other risk factors has been insufficiently addressed. There are some reports on the associations between antipsychotics [11] with ventricular arrhythmias and/or SCA. However, they are usually based on a single geographic area or country. Furthermore, data on trajectories of exposures to different drugs, taking into account duration and dose, are lacking. Clearly, class and drug effects need to be evaluated. Risk stratification algorithms based on findings from epidemiological studies that evaluate traditional risk factors, acquired risk factors, environmental risk factors, and genetic variants *in combination* may aid in the identification of susceptible individuals and subgroups within the population (Fig. 1 right).

Improvements in survival after SCA are possible as new treatment strategies for SCA—in particular focusing on early start of resuscitation procedures—have shown to markedly increase survival rates [12–14]. To date, however, there has not been a large systematic study aimed at comparing the efficacy of the different treatment protocols across Europe and to establish which first-response treatment strategy for SCA offers the highest chance of survival. Importantly, in addition to treatment strategies, patient characteristics and organization of care may further impact on survival, although these factors are poorly considered simultaneously. This integrative approach has important implications as it may help to identify the respective weights of the determinants of survival after SCA and to prioritize necessary improvements. Also, accounting for differences in patients characteristics, treatment strategies and organization of care may help to understand and ultimately reduce the disparities in SCA incidence and survival rates after SCA across Europe and the world [15,16].

To obtain mechanistic insights, studies have focused on discovery of genetic factors on cardiomyopathies and inherited arrhythmia syndromes, which account for 10–15% of SCA in industrialized societies, and have identified relevant pathways [17]. For SCA in the general population, only few genetic analyses have been conducted so far, mostly because sufficiently large DNA collections have been lacking. Most prior studies used a candidate approach on common variants [18] and so far only 2 genome wide association studies on SCA have been performed

by members of the ESCAPE-NET consortium [19,20]. In general, recognizing risk gene (profiles) is of practical importance in clinical decision making, e.g., when a drug with potential arrhythmia risk (e.g., QT prolonging cardiac or noncardiac drugs) must be prescribed to an individual (pharmacogenetics).

Aims

The ESCAPE-NET project (ESCAPE-NET: “European Sudden Cardiac Arrest network—towards Prevention, Education and New Effective Treatments”) has two main objectives: (1) to improve our knowledge of the determinants and mechanisms for the occurrence of SCA, and (2) to improve our capacities to increase the survival after SCA on a European scale.

Its specific aims are:

Towards population cohort integration:

1. To combine Europe's largest deep-phenotyped SCA cohorts for full exploitation of the data
2. To improve and maximize data sharing and stimulate hypothesis-driven research by using new technologies in building and maintaining this large-scale database
3. To develop a financial strategy to keep the database alive after the duration of the project
4. To reach out to other SCA investigators with interest in collaboration and data sharing

Towards prevention:

1. To identify genetic, epigenetic, acquired, and environmental risk factors, and their interactions, for SCA occurrence in a combined large-scale European study population
2. To design a personalized risk score for SCA occurrence
3. To validate the personalized risk score

Towards treatment

1. To relate differences in first-response SCA treatment strategies to survival across different European countries
2. To evaluate effects of novel technologies for SCA treatment by utilizing smartphone applications (for rapid deployment of lay rescuers) and novel technological solutions (e.g., based on ventricular fibrillation [VF] waveform analysis)
3. To design a personalized risk score for survival after SCA

The consortium

The ESCAPE-NET project is funded by the Horizon2020 program of the European Union, and addresses the specific challenges and scope of the Horizon2020 call ‘PM04: Networking and optimizing the use of population and patient cohorts at EU level’. This 5-year project will be performed by a European public-private consortium of 16 partners across 10 EU countries (Fig. 2, Table 1), including academic institutions that provide large patient cohorts, European scientific societies/associations for SCA research who will translate the outcomes into European clinical practice to prevent SCA and improve survival after SCA, and small and medium-sized enterprises who contribute specific expertise. The consortium consists of Europeans key cardiology and emergency medicine departments focusing on SCA, together with expert research departments in the field of Public Health, Ethics, Biomedical Informatics, Epidemiology and Statistics.

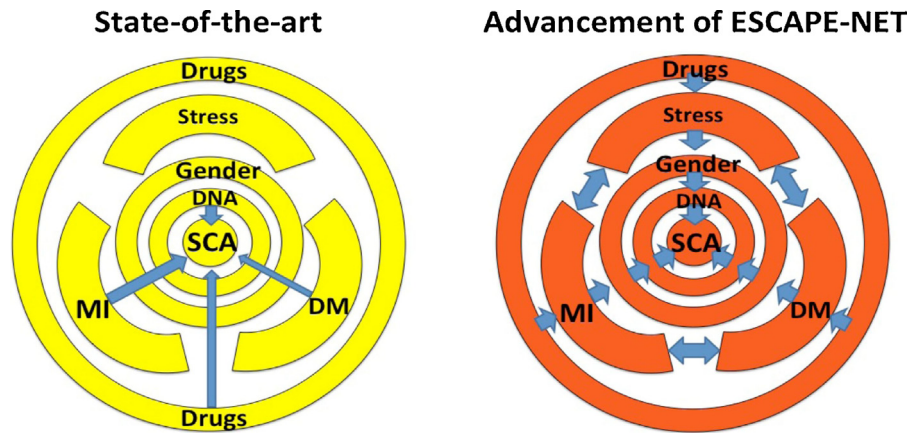


Fig. 1. Risk factors contributing to SCA occurrence (traditional risk factors/comorbidities: DM, diabetes mellitus; MI, myocardial ischemia/infarction).

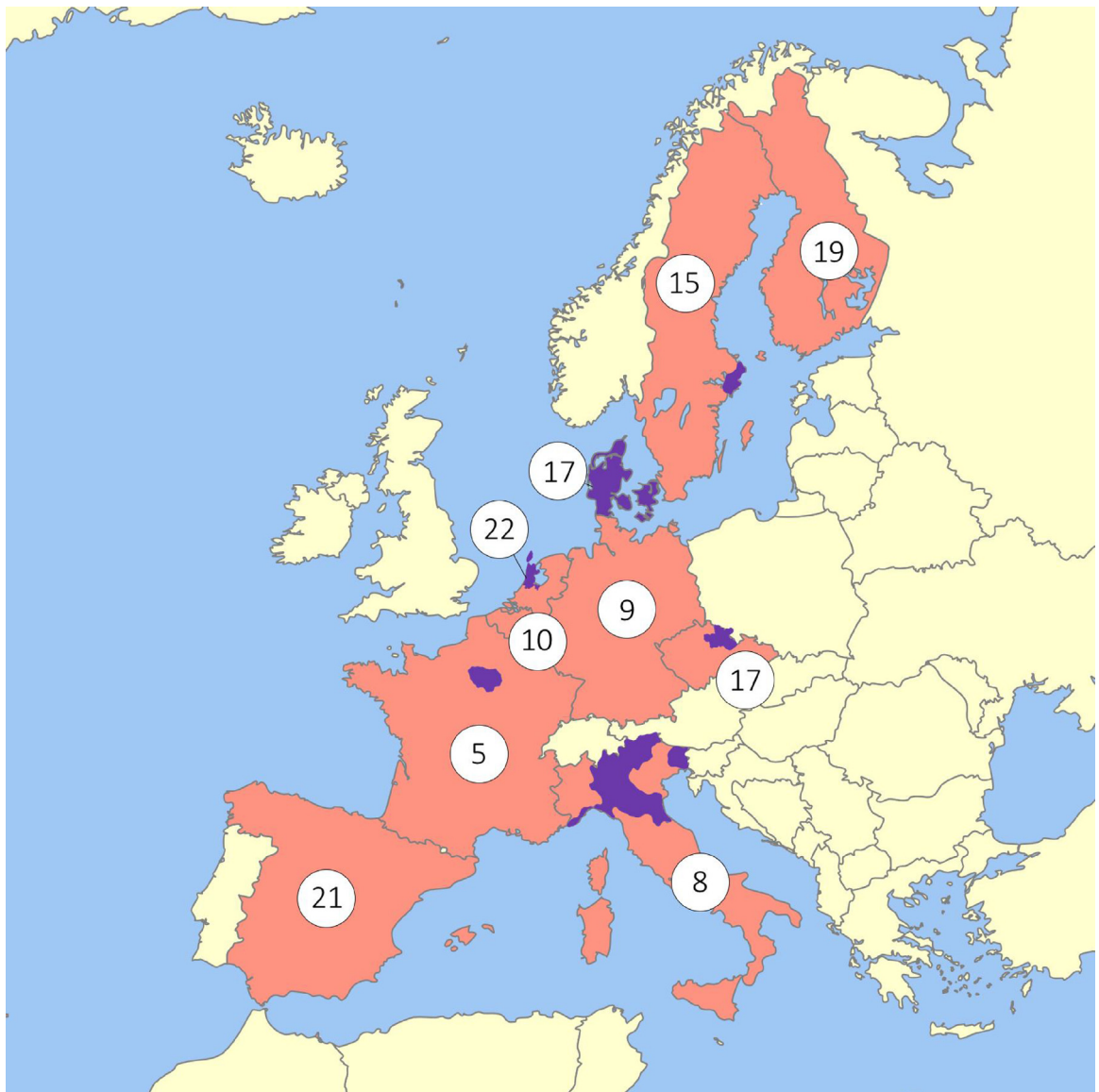


Fig. 2. Large differences in survival rates after SCA across Europe. Countries in orange indicate study sites of ESCAPE-NET; the catchment areas in these countries are indicated in purple. Numbers indicate survival rates (%) at hospital discharge of patients in whom cardiopulmonary resuscitation was attempted as reported in the EuReCa One Registry [16] (survival rates in that registry were analyzed in entire countries or parts thereof). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
The ESCAPE-NET consortium.

Name	Country	Role
<i>Academic partners</i>		
Academic Medical Center (Project Coordinator Dr. Tan)	The Netherlands	Cohort, clinical studies
University of Copenhagen	Denmark	Cohort, clinical studies
Université Paris Descartes	France	Cohort, clinical studies
University of Pavia and IRCCS Istituto Auxologico Italiano	Italy	Cohort, clinical studies
VU University Medical Center	The Netherlands	Cohort, clinical studies
Karolinska Institute	Sweden	Cohort, clinical studies
Emergency Medical Services of the Hradec Kralove Region	Czech Republic	Cohort, clinical studies
Istituto di Ricerche Farmacologiche “Mario Negri”	Italy	Cohort, clinical studies
Helmholtz Zentrum München	Germany	Genotyping
Fundació Institut Mar d'Investigacions Mèdiques	Spain	Pharmacological analysis
<i>European scientific societies/associations for SCA research</i>		
European Society of Cardiology (ESC), representing the European Heart Rhythm Association (EHRA)	France	Dissemination, Education, Implementation
European Resuscitation Council (ERC)	Belgium	Dissemination, Education, Implementation
<i>Small and medium sized enterprises</i>		
Panaxea BV	The Netherlands	Health Economics analysis
BC Platforms Ltd.	Finland	Bioinformatics platform
Catalyze BV	The Netherlands	Project management

Methods

Patient cohorts

ESCAPE-NET contains 11 deep-phenotyped SCA case cohorts totaling 85,790 SCA cases (Table 2) and 5 deep-phenotyped observational prospective population cohorts totaling >50,000 subjects (Table 3). The latter cohorts are of high added importance since they contain detailed information before SCA has occurred, and will be used to study the determinants of SCA occurrence. ESCAPE-NET will also aim for enrichment of the data by linking them to (publicly available) registries, for instance, Statistics Netherlands and Statistics Denmark for collection of socio-economic data.

Data harmonization and integration

A primary step is to make a list of variables which are common to all cohorts based on clinical relevance and availability. Two interconnected data harmonization committees have been created, one for the SCA cohorts and another for the observational prospective population cohorts. As much as possible, the same definitions for exposures/outcomes that were common to each type of cohort were used. Linkage with national claim databases will permit to retrieve trajectories of exposures to different drugs, taking into account duration and dose of exposure to the drug. Furthermore, given the large number of SCA cases, class and drug effects can be evaluated.

Outcome data

The main outcome is SCA in patients with documentation of VF, and sudden cardiac death (SCD) in patients without VF documentation. The same standardized definition for SCD and the same variables required to define it have been adopted in the population and clinical cohorts:

- **Definite sudden cardiac death:** A sudden, natural unexpected death with established time frame from change in cardiovascular status to death:

- Witnessed cases: acute change in cardiovascular status with time to death <1 h
- Unwitnessed cases: a person last seen alive and functioning normally <24 h before being found dead.

- **Probable sudden cardiac death:** Death in a person with cause of death (derived from, e.g., autopsy reports, the National Causes of Death Register, hospital records) likely to be sudden death in an otherwise healthy person free of any chronic and/or severe diseases.

Moreover, information on vital status and related causes of deaths will be obtained by the national registry of the causes of death of each participating country. The neurologic status at hospital discharge will be obtained using the Cerebral Performance category (CPC) [34]. Long-term follow-up is not yet funded, but may be envisaged pending on future funding.

Power

Estimating the required power in a large scale multinational project with various aims and main exposures is a challenging issue. Based on prior experience from consortium members, a minimum of 100 incident cases per cohort is a pre-requisite to conduct multi-variate analysis. As an example, with 118 incident SCA cases among 7773 participants, the Paris Prospective Study I was able to retrieve specific risk factors for SCA in the population, including the discovery that family history of SCA has a strong influence on the risk of SCA in the offspring. (3) Hence, with a total of 85,790 SCA cases, the ESCAPE-NET consortium is expected to be sufficiently powered to address its main objectives.

DNA collection and analysis

DNA collection methods vary between cohorts. The most challenging is DNA collection of non-surviving SCA victims, because postmortem collection of biosamples solely for the sake of research is not allowed in some countries, e.g., the Netherlands; here (ARREST), the solution is to collect biosamples obtained for the

Table 2
SCA cohorts.

Name	Partner	Country	Cause of SCA	SCA cases (N)	DNA samples (N)
ARREST [21]	AMC	NL	all-cause	13786	4473
AGNES [19]	AMC	NL	first myocardial infarction	1023	1023
Cartagene [19]	UP	FR	all-cause	2332	1518
Paris Sudden Death Expertise [22]	UP	FR	all-cause	10093	none
Danish Cardiac Arrest registry [1]	REGIONH	DK	all-cause	47000	6000
SCDY in Denmark [23]	REGIONH	DK	all-cause	1463	140
GEVAMI [24]	REGIONH	DK	first myocardial infarction	1100	1100
Predestination [25]	UPAV, AUXO	IT	first myocardial infarction	341	341
Stockholm Region [26]	KI	SE	all-cause	6100	none
EMS Hradec Kralove Region [27]	EMS	CZ	all-cause	1779	none
RIAC [28]	IRFMN	IT	all-cause	773	none
Total				85790	14595

Table 3
Observational prospective population cohorts.

Name	Partner	Country	Population type	Persons followed (N)	SCA cases (N)	DNA
Paris Prospective Study 3 [29]	UP	FR	general population	10157	130	3800
Copenhagen City Heart Study [30]	REGIONH	DK	general population	24000	2000	none
Hoorn studies [31]	VUMC	NL	general population	5237	190	3953
Diabetes Pearl [32]	VUMC	NL	diabetes mellitus	6666	to be determined	6666
Diabetes Care System [33]	VUMC	NL	diabetes mellitus	7000	240	6000
Total				53060	2560	20419

sake of patient care which are left over and would otherwise be discarded (blood samples, endotracheal tubes). To maximize standardization, all DNA analyses are conducted by one partner (Helmholtz Zentrum München) using the Illumina Global Screening Array which contains >770,000 SNPs, and deep-sequenced datasets as reference panels for imputation, e.g., Haplotype Reference Consortium. Hence, a database of an estimated >9 million variants (3.6 times larger than the number of variants in the most recent genome-wide association study on SCA [20]) in >15,000 SCA samples will be available for genetic association. This will allow a genome-wide assessment of common genetic variants and an assessment of the role of rare variants within genes from selected pathways based on a hypothesized (patho)physiological role. The ESCAPE-NET consortium has the added ability to study the magnitude of the functional effect in the pipeline of functional and translational studies conducted at the Laboratory of Experimental Cardiology of AMC, of which the Project Coordinator is part [35]. Network analysis of the findings from the genetic studies will be conducted with the aim of discovering proteins and pathways that may provide the basis for novel prevention and treatment strategies and/or drug design.

Investigating first-response treatment for SCA and survival across europe

The ESCAPE-NET consortium has the opportunity to perform a large systematic study aimed to compare the efficacy of the different treatment protocols across Europe. As an innovation, the contribution of first-response treatment strategy will be estimated taking into account inherited, acquired, socio-economic, and environmental factors. Several options are available to compare the efficacy of treatment strategies. One is to relate change in survival rate to change in resuscitation strategy. Another is to compare survival rates between study sites and see whether differences relate to different resuscitation strategies between those sites. Interestingly, survival comparisons before and after the ERC 2015 International Guidelines for the treatment of an SCA victim could be undertaken. Finally, recent studies have led to the hypothesis that detailed analysis of VF waveforms over time such as amplitude spectrum area, could provide prognostic information for both the success of defibrillation and clinical outcomes [36]. Accordingly,

under the umbrella of ESCAPE-NET, the «AMplitude Spectrum Area to guide defibrillation during cardiopulmonary resuscitation in out-of-hospital cardiac arrest patients»-AMSA trial, a multicenter randomized clinical trial, will be conducted to test this hypothesis.

Health economics analysis

The effect of implementation of the use of most-effective first-response treatment will be assessed. A comprehensive health economic model is used for this purpose, and sensitivity analyses are used to propagate uncertainty in the input data to the model outcomes. Several relevant scenario analyses are performed to further enhance the understanding of the relation between characteristics of the most-effective first response treatment and its health economic impact. To gain insight into the costs and benefits of first-response treatment programs, the costs of the program itself will be assessed (e.g., development of app-system, implementation schemes), but also potential savings in health care costs. In-hospital health care parameters will be compared (i.e., SCAs involving lay rescuers vs. emergency medical services only, per type of program), analyzing costs of hospital transport, duration and cost of admission in hospital, diagnostics and interventions [37]. Costs will be measured from the perspective of society and extrapolated after the first year.

Building risk prediction models for SCA occurrence and for SCA survival

The ESCAPE-NET consortium will develop and validate risk scores predicting occurrence of SCA and survival after SCA, using the same methodological approach. The first step will be to identify significant predictors using Cox proportional hazard models. Given the number of potential candidates and the variety of dimensions (including clinical variables, socio-economic factors, drugs), we will first identify predictors within each dimension and then enter them into a single multivariate model. As usual, 2 by 2 interactions between the retained variables will be investigated. Second, we will evaluate the performances of the model assessing (a) calibration (b) the discrimination of the model using the Harell's C index adapted to censored data. Reclassification analysis (Net Reclassification index, Integrated Discrimination Improvement) could also

be used in case we wish to assess the added value of a specific covariate (e.g., depression) above a set of more traditional covariates [38]. For validation, several options are available: (1) within ESCAPE-NET, develop the model in a derivation set (i.e., in 2 cohorts combined) and validate it in the remaining cohorts (validation set); (2) use all ESCAPE-NET cohorts to derive the model and perform external validation through international collaborations pending on the availability of the covariates in these validation cohorts (i.e., the case for genetic data); (3) use all ESCAPE-NET cohorts to derive and validate the model (internal validation) using cross-validation methods and penalization procedures to correct for over-optimism.

Governance and collaborations

An Executive Committee has been created along with a Collaboration Policy document, which includes sections on quality control, publication rules, and ways to solve possible conflicts. One section deals with collaborations within and outside of the consortium and proposals for joint research from inside and outside of the consortium. At present, collaborations with some US cohorts are already in place and will be continued, including the Physicians Health study, the Nurses Health study, the Oregon registry, and the CHARGE consortium [20].

Discussion

The aim of the ESCAPE-NET project is to maximize the exploitation of major deep-phenotyped European SCA cohorts by bringing them together in one joint database of 85,790 SCA cases. This will generate the power necessary to unravel the complex causes of SCA with the strategy of a multi-scale approach, ranging from genomics to the socio-economic environment of each individual in the community. This will form the foundation of a personalized risk score, and the development of effective individualized prevention and treatment strategies. As treatment of SCA (particularly first-response treatment) is different between European countries, combining the large cohorts that are present across Europe additionally creates the opportunity to evaluate and compare treatment strategies.

Large nationwide registries such as in Japan [39] or binational (USA and Canada) registries such as the EPISTRY registry [40] exist. Although these may already investigate heterogeneity of risk factors, clinical management and prognosis, we believe that with its multinational design, these aspects may be expanded and refined within ESCAPE-NET. In addition and beyond these Japanese and North-American registries, biosamples are available in ESCAPE-NET and genotyping is already funded (genome-wide association studies) and planned (whole-exome sequencing). Still, the availability of these registries outside Europe provides ESCAPE-NET excellent opportunities for collaborations and international comparisons.

At the European level, the European Registry of Cardiac Arrest project (EuReCa) provides a detailed overview on epidemiology, treatment and outcome of patients suffering out-of-hospital SCA in 27 European countries. EuReCa One was a 1-month survey of 10,000 such cases [16], while EuReCa Two, which has commenced on 1 October 2017, will be a 3-months survey with a special focus on lay resuscitation. Similar to the Japanese and North-American registries, biosamples are not available in the EuReCa surveys. Likewise, these registries are not designed with the specific aim of evaluating risk factors for occurrence of SCA as opposed to the deeply phenotyped cohorts of ESCAPE-NET.

Limitations

We recognize the following limitations. Firstly, despite the harmonization of the variables and outcome definitions, some degree of heterogeneity will remain. As a corollary, some important variables are not available in all cohorts. For these cohorts, subgroup analysis only can be conducted. Secondly, in these observational cohorts, causality can be suggested but not established. Thirdly, despite the size of the consortium, not all European countries are represented so that the picture may not be representative for the entire European population. However, ESCAPE-NET is a dynamic project with the specific aim of reaching out and inviting other cohorts/registries to join or collaborate with the consortium. Finally, despite the already wide spectrum of areas covered by ESCAPE-NET, additional and important areas deserve future consideration. For instance, omics analysis could be conducted in subgroups pending on future obtained grants. In particular, the availability of large biobanks in all observational prospective population cohorts offers the possibility to identify circulating biomarkers for the occurrence of SCA. Also, long-term follow-up of neurologic/functional status is an important aspect to study.

Conclusion

ESCAPE-NET has a broad scope and will make major contributions to understanding SCA on all levels. This will not only impact direct patient care (development of individualized novel preventive and therapeutic strategies for SCA), but also the organization of out-of-hospital and in-hospital health care in Europe. Moreover, it will have public health implications, and establish a lasting framework for future basic and clinical scientific investigations.

Conflict of interest

The authors declare no conflict of interest.

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